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Case Report

Perampanel in lissencephaly-associated epilepsy

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ABSTRACT

We retrospectively investigated whether perampanel (PER) could serve as an alternative for treating drug-resistant seizures in lissencephaly. We investigated the following data: age at onset of epilepsy, age at start of PER, etiology, brain MRI findings, seizure type, seizure frequency, adverse effects, and concomitant anti-epileptic drugs. There were 5 patients with lissencephaly, including 2 with Miller–Dieker syndrome. Four out of five patients exhibited ≥50% seizure reduction. Myoclonic seizures disappeared in 1 patient. PER was an effective adjunctive anti-seizure drug in our series of patients with lissencephaly.

1. Introduction

Alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptors have long been suggested to play an important role in ictogenesis and epileptogenesis [1]. Perampanel (PER) is a selective noncompetitive AMPA receptor antagonist that was developed for the treatment of epilepsy. PER does not inhibit N-methyl-D-aspartate (NMDA) receptors, a different class of ionotropic glutamate receptors. Recently, it has been reported effective for the treatment of various epileptic disorders, including Lennox–Gastaut syndrome; it has been effective for treatment of myoclonic seizures, such as progressive myoclonus epilepsy; Lafora disease [2], dentatorubral–pallidoluysian atrophy (DRPLA) [3] and Unverricht–Lundborg disease [4].

Neuronal migration disorders include lissencephaly, pachygyria, subcortical band heterotopia (SBH), and periventricular nodular heterotopias, which are rare brain malformations caused by defective neuronal migration during embryonic development. Complete cortical disorganization results in lissencephaly, which typically manifests with drug-resistant epilepsy. Seizures occur in >90% of children; most children have multiple seizure types including persisting spasms, focal seizures, tonic seizures, and atonic seizures [5]. Most cases of daily seizures are a burden to both patients and caregivers; they commonly fail to exhibit seizure control, despite the use of many anti-seizure drugs for the resolution of seizures [6].

We retrospectively investigated whether PER could serve as an alternative for treating drug-resistant seizures in lissencephaly.

2. Case report

We retrospectively surveyed patients with lissencephaly who were treated with PER at the Saitama Children's Medical Center from 2016 to 2018. A total of 5 patients (4 boys, 1 girls) were included in this study. We retrospectively collected the following clinical data: age at the onset of epilepsy, age at the start of PER, etiology, brain magnetic resonance imaging (MRI) findings, seizure types, seizure frequency before and after PER administration, adverse effects, and concomitant anti-seizure drugs used at the start of PER. PER was administered at 0.04 mg/kg/day, and was increased at 2–4-week intervals. In this study, drug efficacy was defined as ≥50% seizure reduction rate at 3 months from the start of PER. Seizure frequency was observed by caregivers in daily life and finally assessed by a pediatric epileptologist.

Since 2016, PER has been approved for use in Japan in patients with epilepsy who are >12 years of age; it can be used for the adjunctive treatment of primary generalized tonic–clonic seizures (GTCS) and partial-onset seizures. Therefore, informed consent was obtained from the parents or guardians of each patient. For patients <12 years of age, we explained the nature of the study and obtained age-appropriate assent. This study was approved by the Saitama Children's Medical Center Institutional Review Board [2018-03-05].

Clinical data of 5 patients with lissencephaly are shown in Table 1. The median age at onset of epilepsy was 2 months (range: 1 month–6 months). Median age at the start of PER was 7 years, 4 months (range: 2 years, 6 months–16 years, 1 month). Five patients with lissencephaly included 2 with Miller–Dieker syndrome. Gene analysis was performed in 2 patients, 1 with LIS-1 deletion associated with

Abbreviations: AMPA, alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid; DRPLA, dentatorubral–pallidoluysian atrophy; GTCS, generalized tonic–clonic seizures; NMDA, N-methyl-D-aspartate; PER, perampanel.

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Table 1
Clinical profiles of patients.

Patient no./sex	Etiology	Age at epilepsy onset	Age at the start of PER	Seizure type	Seizure frequency		Concomitant medication	Adverse effect
					Before PER	After PER		
1/F	MDS	6 m	7 y 4 m	GT	20/d	10/d	VPA, PB	Respiratory failure
2/M	MDS	1 m	7 y 10 m	GT	10/d	2/d	VPA, LEV, TPM, KBr	Sedative effect
3/M	LIS-1	2 m	2 y 6 m	GT	10/d	10/d	VPA, PHT, ZNS	
4/M	Unknown	2 m	4 y 0 m	GT	5/d	1/d	PB, CZP	
5/M	Unknown	4 m	16 y 1 m	GT	5/d	2/d	VPA, TPM, CZP	
				Myoclonic sz	3/m	0/m		

Perampanel, PER; CZP, clonazepam; d, day; GT, generalized tonic seizure; KBr, potassium bromide; LEV, levetiracetam; m, month; MDS, Miller–Dieker syndrome; PB, phenobarbital; PHT, phenytoin; sz, seizure; TPM, topiramate; VPA, valproic acid; w, week; ZNS, zonisamide.

lissencephaly, and 1 in whom the short arm of chromosome 17 was monosomic; FISH analysis confirmed G-banding indicative of Miller–Dieker syndrome. All patients, except patient no. 3, exhibited ≥50% seizure reduction (4/5). Notably, myoclonic seizures were effectively managed in patient no. 5. Adverse effects included respiratory failure in 1 patient and mild sedation in 1 patient. Brain MRI was performed in all patients and is shown in Fig. 1.

3. Discussion

In this retrospective cohort study, PER was effective in the treatment of patients with lissencephaly. A 50% responder rate (50% RR; i.e., at least 50% seizure reduction upon administration of PER) of PER was observed in 4 of 5 patients (80.0%) in our study. A prior adult study reported that the efficacy (50% responder rate) of PER in patients with primary GTCS was 64.2% [7]. Patients with lissencephaly typically exhibit drug-resistant daily seizures. Drug-resistant seizures are a burden to both patients and their caregivers. Most patients with lissencephaly commonly fail to exhibit seizure control, despite the use of many anti-seizure drugs for the resolution of seizures [6]. This case series demonstrated a response to PER in patients with lissencephaly. Interestingly, 1 patient (patient 5) exhibited improvement of daily activities and motor development, including rolling over, and spontaneously began to vocalize. A case report of patients with DRPLA revealed seizure improvement and recovery of activities of daily living [2]. PER might have effects on activities of daily living other than seizure reduction, including for treatment of myoclonic seizure [2–4]. One patient exhibited epileptic myoclonus in our study and was effectively treated with PER.

It is important to consider the mechanism by which PER is effective for the treatment of neuronal migrational disorders. Many reports have surveyed neuronal migration, which is affected by a variety of factors [8]. Glutamate plays an essential role in neuronal migration. Glutamate receptors consist of ionotropic receptors: NMDA, AMPA, kainic, and metabolic receptors. AMPA receptors, but not NMDA receptors, are involved in neuronal migration. AMPA receptors play a key role in neuronal migration [9]. Functional AMPA receptors are reportedly expressed by tangentially migrating interneurons in the developing brain, while metabotropic glutamate receptor primarily appears in radial glial cells [10]. Neurons involved in lissencephaly are thought to be immature migrating cells. PER has recently been shown to act on the AMPA receptor. In this context, PER could selectively affect AMPA receptors in immature migrating interneurons, whereas other anti-seizure drugs with other functional mechanisms, including those that use NMDA receptor blockage, may not be effective for patients with lissencephaly. Moreover, a report of the rat kindling model showed that the anti-ictogenic effect of PER is stronger in immature brain [11]. The authors speculated that low expression of the GluA2 subunit of the AMPA receptor in immature neurons may contribute to this effect. AMPA receptors may exhibit a specific phenotype in neuronal migration disorder, which may explain why PER, an AMPA receptor antagonist, may be effective for treatment of lissencephaly.

Adverse effects of PER are largely mild or moderate in severity [12]. Two of 5 patients (40.0%) exhibited adverse effects: sedative effects in 1 patient and respiratory failure in 1 patient. Neuronal migration disorder and complications, concomitant drug treatment, sedative effects and respiratory failure, in the context of the underlying disease, may readily occur in a variety of situations. We regard the PER sedative effect as

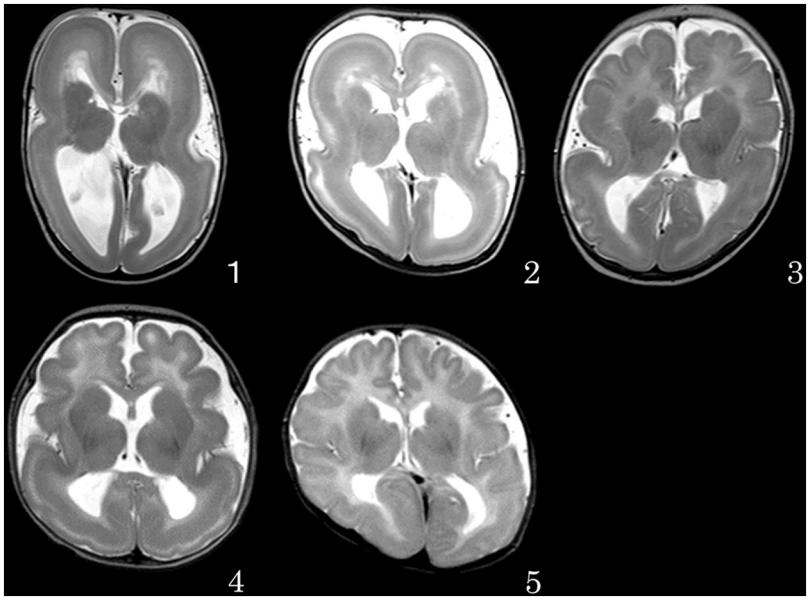

Fig. 1. Representative brain magnetic resonance imaging (MRI) findings in T2-weighted images. Each number indicates patient number in Table 1.

mild. Indeed, sedative effects and respiratory failure in those patients resolved soon after discontinuation of PER.

A principal limitation of this study is the small number of patients. However, neuronal migrational disorders are relatively rare. In addition, evaluation of anti-seizure drugs was limited to the subjective assessments of seizure frequency dependent on observations by caregivers. Moreover, the mechanism underlying the effectiveness of PER for lissencephaly-associated epilepsy is unknown. Therefore, our study findings are preliminary, and we speculate that PER may be effective.

In conclusion, PER was an effective adjunctive anti-seizure drug in our series of patients with lissencephaly.

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Declarations of interest

None.

Ethical statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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